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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,227	10/03/2003	Hiroaki Ito	053466-0365	8597

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EXAMINER	
MERTZ, PREMA MARIA	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/677,227	ITO ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 22-47* is/are pending in the application.

4a) Of the above claim(s) *1-19, 22-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

Claims 1-19, 22-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Amended claim 43 (10/31/07) and previous claims 44-47 are pending and under consideration by the Examiner.

Claim rejections-35 USC § 112, scope of enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2a. Claims 43-47, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating inflammatory bowel disease by administering an effective amount of monoclonal antibody, PM-1 or MR16-1 against the human IL-6 receptor, does not reasonably provide enablement for a method of treating all inflammatory diseases by administering "all" interleukin-6 receptor antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record set forth at pages 3-7 of the previous Office action (12/5/2006) and page 3 (8/15/07).

The specification delimits the instant method to administering antibodies PM-1 and MR16-1 for treatment of inflammatory bowel disease) (see page 5, lines 9-34), however, claim 43 as amended recites a method for treating all inflammatory diseases, comprising administering an IL-6 receptor antibody.

Claim 43 is drawn very broadly to methods of treating all inflammatory conditions by administering IL-6 receptor antibodies. Applicants argue that the specification teaches that inflammatory diseases are treated by blocking the signal transduction from IL-6 with an anti-IL-6 receptor antibody, which inhibits the biological activity of the IL-6 receptor and that a person of ordinary skill in the art would understand this mechanism and know that other anti-lL-6 receptor antibodies, besides PM-1 or MR16-1, which bind to the interleukin-6 receptor, block signal transduction by IL-6 and inhibit the biological activity of IL-6 could also be used for the treatment of inflammatory diseases in general. However, contrary to Applicants arguments, other than the disclosure of Example 4, pages 39-41 of the specification in which the role that antibodies PM-1 and MR16-1 play in inhibiting the binding of IL-6 to the IL-6 receptor, the specification fails to provide any guidance for the successful treatment of all inflammatory conditions in vivo by using IL-6 receptor antibodies.

There is no disclosure in the instant specification to enable practice of the invention as claimed, i.e. administration of IL-6 receptor antibodies to treat inflammatory diseases which encompasses acute inflammatory demyelinating polyradiculoneuropathy, chronic inflammatory

diseases, such as rheumatoid arthritis, inflammatory bowel disease (Crohn's disease), systemic lupus erythematosus, multiple sclerosis, ulcerative colitis, shoulder tendonitis or bursitis, gouty arthritis, polymyalgia rheumatica and type 1 diabetes. Furthermore, chronic inflammation can be produced by microorgainisms such as *Mycobacterium tuberculosis*, *Actinomycetes*, and numerous fungi, protozoa and metazoal parasites. Such organisms are in general able to avoid phagocytosis or survive within phagocytic cells, and tend not to produce toxins causing acute tissue damage. Resolution of the various complications in regards to using an IL-6 receptor antibody protein as a therapeutic agent for inflammation is highly unpredictable. One of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of pharmaceutical formulations of the IL-6 receptor antibodies as a therapeutic agent, and symptoms to correlate with inhibition of the condition. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention claimed.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed method of using all IL-6 receptor antibodies as therapeutic agents in a patient other than for treating inflammatory bowel disease. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a given a protein as a therapeutic agent for treating all inflammatory conditions *in vivo* based solely on *prophetic suggestion* as highly problematic (see MPEP §2164.02). Furthermore, the specification would not be considered enabling since the state of protein aggregation is highly unpredictable. The

factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The method of the instant claims comprises the administration of all IL-6 receptor antibodies for treating all inflammatory diseases. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Given the inherent unpredictability of physiological activity, which would include biological processes, i.e., methods of treatment, a certain amount of enablement beyond mere assertion must be required.

Furthermore, the specification is non-enabling for a method of treating all inflammatory diseases in a patient by administering all IL-6 receptor antibodies, as recited in claim 43 because to practice such a method would require knowledge of the route, duration and quantity of administration of that protein to a subject for each of the diseases, and this information is not provided by the instant specification. The text on pages 28-29 of the instant specification clearly fails to supply the guidance that would be needed by a routine practitioner. The instant specification has also failed to disclose how these parameters are to be determined, how a similar method was practiced in the art with a different agent or to provide even a single working example, prophetic or actual of the claimed method. In the absence of this guidance, a practitioner would have to resort to a substantial amount of undue experimentation involving the variation in the amount and duration of administration of the antibodies of the instant invention and in determining a suitable route of administration. The instant situation is directly analogous to that which was addressed in In re Colianni, 195 U.S.P.Q. 150, C.A.F.C., which held that a "disclosure that calls for application of 'sufficient' ultrasonic energy to practice claimed method of fusing bones but does not disclose what 'sufficient' dosage of ultrasonic energy might be or how those skilled in the art might select appropriate intensity, frequency, and duration, and contains no specific examples or embodiment by way of illustration of how claimed method is to be practiced does not meet requirements of 35 U.S.C. § 112 first paragraph".

Therefore, a method for treating all inflammatory diseases such as rheumatoid arthritis would be non-enabled because the cause of the disorder to date remains unclear.

With respect to claims 43-47, as recited, what is claimed in the instant invention broadly encompasses a method of administering "all" IL-6 receptor antibodies. While the specification discloses that a "IL-6 receptor antibodies" (see page 5) is "preferably" PM-1 or MR16-1 that

binds to IL-6 receptor and inhibits binding of IL-6 to its receptor and this is the biological property which the administered compound is expected to exhibit, the specification is non-enabling for the unlimited number of compositions encompassed by the scope of the claims. Claim 43 for example, is a single means claim (M.P.E.P. 2164.08(a)). In In re Hyatt, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), the Courts have held that: "A single means claim, i.e. where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph." (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor). Since no material limitations for the IL-6 receptor antibody have been recited in the claim and only a biological activity has been recited, the claim encompasses every conceivable structure (means) for achieving the stated property (result), a fact situation comparable to Hyatt. The claimed invention encompasses a method of administering compositions not envisioned or described in the specification, and neither does the specification disclose how these claimed compositions can be distinguished from each other. The specification only enables treating inflammatory bowel disease by administering PM-1 or MR16-1 antibodies, the antibodies having specific characteristics and properties. These properties may differ structurally, chemically and physically from other known proteins. By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which other

IL-6 receptor antibodies to be administered are encompassed by the scope of the claims is practically infinite and the guidance provided in the specification very little, thereby rendering the results of the methods taught in the specification unpredictable (see pages 39-41). Therefore, it would require undue experimentation to determine which other IL-6 receptor antibodies to be administered in the claimed method would be encompassed by the scope of the claims. The disclosure of the two IL-6 receptor antibodies, is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims, which encompass administering every and all IL-6 receptor antibodies for treatment of all inflammatory conditions . In In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), the Courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Furthermore, the amount of embodiments corresponding to the desirable compositions in the claimed method, may be innumerable, and the enabled embodiments amount to only two. Therefore, there are substantial scientific reasons to doubt the scope of enablement, as set forth above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe treatment of a disease other than rheumatoid arthritis by administering PM-1, and MR16-1 antibodies, and since it is deemed to constitute undue experimentation to determine all the others, the disclosure is not commensurate with the scope of the claims. It is suggested that by employing conventional claim language, the claims be amended to include the specific antibodies supported by the instant specification in the claimed method.

The following reference is cited herein to illustrate the state of the art with respect to antibodies:

Chuntharapai et al. (1997) note that the vast majority of antibodies are not antagonistic and that antibodies have to be screened to determine their ability to bind to human neutrophils (see page 21, second para). The reference also discloses that blocking activities of monoclonals when compared show disparate blocking on ligand binding and inhibition of ligand binding or no inhibition at all (see page 24, last 2 lines; page 25).

Claim rejections-35 U.S.C. 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 43-47, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 is vague and indefinite because it recites "inflammatory diseases'. The metes and bounds of this term are unclear because the term encompasses inflammatory diseases ranging from rheumatoid arthritis to multiple sclerosis. It is suggested that the claim be amended to recite the inflammatory disease intended to be claimed.

Claim 47 recites the limitation "the inflammatory bowel disease" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claims 44-46 are rejected as vague and indefinite insofar as they depend on the above rejected claim 43 for their limitations.

Claim rejections-35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4a. Claims 43-44, 47, are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 96/38481.

This rejection is maintained for reasons of record set forth at pages 12-13 of the previous Office action (12/5/2006) and pages 4-5 of the previous Office action (8/15/2007).

Applicants argue that the '481 reference teaches that blocking of all gp 130-related signals is useful for treatment of inflammatory diseases and that the present invention treats inflammatory bowel diseases through blocking only the IL-6 related signal. However, contrary to Applicants arguments, claim 43 recites "comprising" which is open language. Therefore, the method of treating inflammatory diseases as encompassed by the instant claims, is not specific to blocking a signal only through the IL-6 receptor but also encompasses blocking a signal via the other receptors i.e. leukemia inhibitory factor, ciliary neurotrophic factor, oncostatin M and cardiotrophin-1 receptors. Therefore, from the instant claims one of ordinary skill in the art would conclude that the instant antibody used in the claimed method not only blocks IL-6 signal transduction but possibly the signal transduction via the leukemia inhibitory factor, ciliary neurotrophic factor, oncostatin M and cardiotrophin-1 receptors. Therefore, the reference anticipates instant claims 43-44, 47.

4b. Claims 43-44 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,888,510 ('510 patent).

The '510 patent teaches a method of treating an IL-6 mediated disease such as rheumatoid arthritis by administering an IL-6 receptor antibody (see column 13-14, Example 2; column 14, claims 6-11). Thus the '510 patent anticipates instant claims 43-44.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5a. Claims 43-47 are rejected under 35 U.S.C. § 103 as being unpatentable over WO 96/38481 in view of Queen et al. (U.S. Pat No. 5,530,101).

This rejection is maintained for reasons of record set forth at pages 13-14 of the previous Office action (12/5/2006) and pages 5-6 of the previous Office action (8/15/2007).

Applicants argue that the Queen reference teaches the production of antibody fragments, including the FAB fragment and the production of chimeric antibodies and the humanization of monoclonal antibodies as well as designing a humanized antibody that retains affinity for its antigen and that nothing in this reference suggests using an antibody fragment of an anti-interleukin-6 receptor to treat inflammatory bowel disease. Applicants also argue that the '481 reference does not teach, suggest or motivate one of ordinary skill in the art to treat inflammatory bowel disease through blocking the IL-6 receptor alone and accordingly applicants request the examiner withdraw this rejection and allow the new claims 43-47. However, as argued by the Examiner in paragraph 4a above, since claim 43 recites the term "comprising", this language encompasses treating inflammatory diseases such as inflammatory bowel diseases by blocking a signal via the other receptors i.e. leukemia inhibitory factor, ciliary neurotrophic factor, oncostatin M and cardiotrophin-1 receptors. Therefore, reference '481 in view of Queen '101 renders obvious claims 43-47.

5b. Claims 43-47 are rejected under 35 U.S.C. 103(a) as unpatentable over U.S. Patent No. 5,888,510 ('510 patent) in view in of Queen et al. (U.S. Patent No. 5,530,101).

The disclosure of the '510 patent has been set forth above (see paragraph 4b above). However, the '510 reference does not disclose administering humanized antibodies to IL-6R.

Queen et al., (column 13, lines 5-65) teaches the humanization of monoclonal antibodies, as well as the issues involved in designing a humanized antibody that retains high affinity for its antigen. Queen et al., (column 17, lines 31-43) further teaches the production of antibody fragments, including the Fab fragment.

Therefore, at the time the invention was made, it would have been prima facie obvious to a person of ordinary skill in the art to obtain humanized antibodies as taught by Queen et al, to the IL-6R protein as taught by '510 for the treatment of inflammatory diseases such as inflammatory bowel disease. The motivation for doing so would have been the decreased immunogenicity of humanized antibodies when injected into humans, while the humanized antibodies retain their affinity for their epitope (Queen et al., (column 2, lines 5-8)).

Conclusion

No claim is allowed.

Claims 43-47 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Prema Mertz/
Primary Examiner
Art Unit 1646